DIAGNOSTIC CHALLENGE

Fatigue, weakness, anemia and hypercalcemia in a 63-year-old woman

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Case presentation

A 63-year-old woman was admitted to the Royal Victoria Hospital in October 1978 because of fatigue, weakness and anorexia. She had noticed the onset of progressive weakness, fatigue and dyspnea on exertion 7 months earlier. She had lost 11 kg but attributed this to a weight reduction regimen. She also complained of vague, fleeting pains in the left axilla and left upper quadrant of the abdomen. A physician she consulted felt she probably had a functional disorder and referred her to a cardiologist, who, after obtaining a history that suggested ischemic heart disease, treated her for angina.

Her symptoms persisted and, 5 months before admission, anemia was noted at a routine clinic visit. It was attributed to bleeding from a colostomy created 4 years previously because of a strangulated umbilical hernia. Subsequently a right hemicolectomy was performed and the colostomy was closed. Pathological examination of the resected colon revealed a lipoma and four adenomatous polyps of the right colon. A carcinoembryonic antigen level of 4.6 ng/dl (normal range 0 to 2.5 ng/dl) was noted.

Following her recovery from the operation the patient's weakness and fatigue worsened, her left axillary pain occurred more frequently and she began to have a nonproductive cough. A chest roentgenogram, taken while she was an outpatient, revealed right hilar lymphadenopathy, a nodule in the periphery of the lower lobe of the left lung and a left-sided pleural lesion, whereas a roentgenogram obtained at the time of the colectomy had been normal. She was therefore admitted to hospital for investigation.

She was pale and thin. Her pulse rate was 76 beats/min, her blood pressure 130/80 mm Hg, her respiratory rate 20/min and her temperature 37°C. Physical examination revealed the following abnormalities: a grade 2/6 systolic murmur along the left sternal border, mild tenderness in the right upper quadrant of the abdomen, a large umbilical hernia, multiple surgical scars, and tenderness to percussion of the cervical and thoracic regions of the spine as well as the left anterior ribs. The patient was taking insulin for diabetes mellitus diagnosed 1 year previously, as well as propranolol, nitroglycerin and iron.

The hemoglobin concentration was 10 g/dl, the hematocrit 30%, the mean corpuscular volume 80 fl, the mean corpuscular hemoglobin 1.61 fmol (26 pg) and the mean corpuscular hemoglobin concentration 21.1 mmol/l (34 g/dl). The following counts were recorded: reticulocytes 3.2%, platelets 210 × 10^9/l and leukocytes 8.3 × 10^9/l, with a normal differential. A blood smear showed abnormal variation in the size and shape of the erythrocytes and rouleau formation. Urinalysis indicated 3+ proteinuria (a high level), a trace of blood and occasional granular casts. Analysis of the serum showed the following concentrations: glucose 8.7 mmol/l (156 mg/dl), bilirubin 8.6 μmol/l (0.5 mg/dl), urea nitrogen 6.1 mmol/l (17 mg/dl), creatinine 88.4 μmol/l (1.0 mg/dl), calcium 2.9 mmol/l (11.9 mg/dl), phosphate 1.3 mmol/l (4.1 mg/dl), albumin 29 g/l, total protein 60 g/l, sodium 135 mmol/l, potassium 4.5 mmol/l, chloride 96 mmol/l, total carbon dioxide 32 mmol/l, alkaline phosphatase 636 IU/l, glutamic oxaloacetic transaminase 31 IU/l, glutamic pyruvic transaminase 60 IU/l and lactic dehydrogenase 122 IU/l. The prothrombin and partial thromboplastin times were normal. Bence Jones proteinuria was not found but serum protein electrophoresis showed a mild polyclonal increase in the concentration of immunoglobulins. A chest roentgenogram again showed right hilar lymphadenopathy and a small peripheral nodule in the lower lobe of the left lung (Fig. 1). There was a pathologic fracture of the sixth left rib and destruction of the pubic ramus. Roentgenography after a barium enema and sigmoidoscopy

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showed no lesions. An intravenous pyelogram showed that the left kidney was displaced downward and its upper calyces were rotated laterally (Fig. 2). Abdominal ultrasonography showed a large mass in the area normally occupied by this kidney. Bone marrow aspiration and biopsy revealed no tumour cells. Tests of thyroid function and measurement of the serum cortisol concentration gave normal results, as did electrocardiography.

The patient's condition gradually deteriorated; her thinking became paranoid and she refused medications and food. Three weeks after her admission to hospital she died.

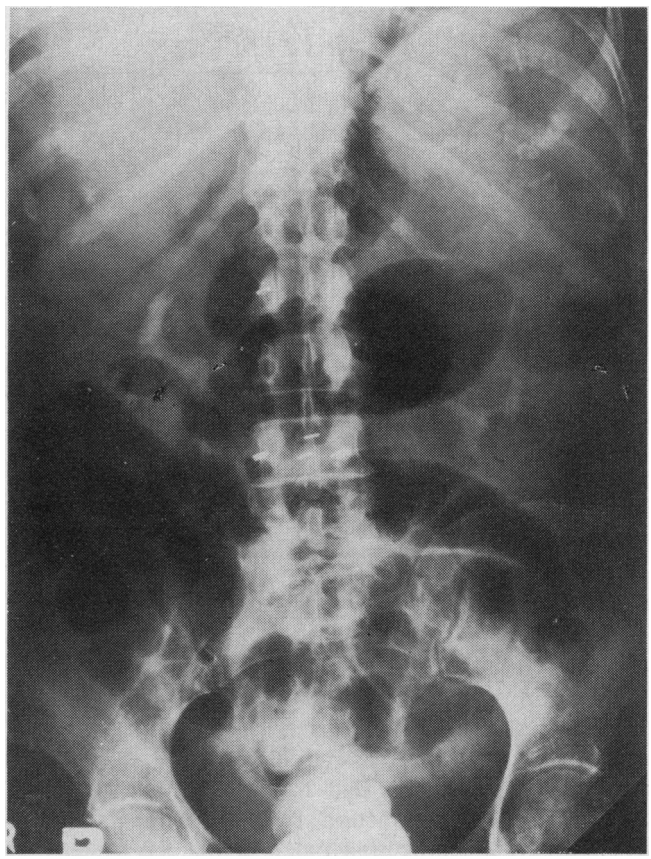

FIG. 2—Displacement of left kidney by mass, and bony destruction of pubic ramus.

Differential diagnosis

Dr. Gelston: This case may be approached by reviewing the laboratory data, beginning with the hypercalcemia. The most common cause of hypercalcemia in hospitalized patients is cancer, although a variety of nonmalignant syndromes may be responsible for the abnormality (Table I).

Malignant disease can cause hypercalcemia through several mechanisms. Frequently the destruction of bone by metastatic disease causes an increase in the serum concentrations of both calcium and phosphate, although the phosphate level may be normal or low in malnourished individuals. Osteolytic metastases have been reported in patients with carcinoma of the breast, lung, kidney, thyroid, prostate or bladder, as well as in those with lymphoma. In about 15% of cases of

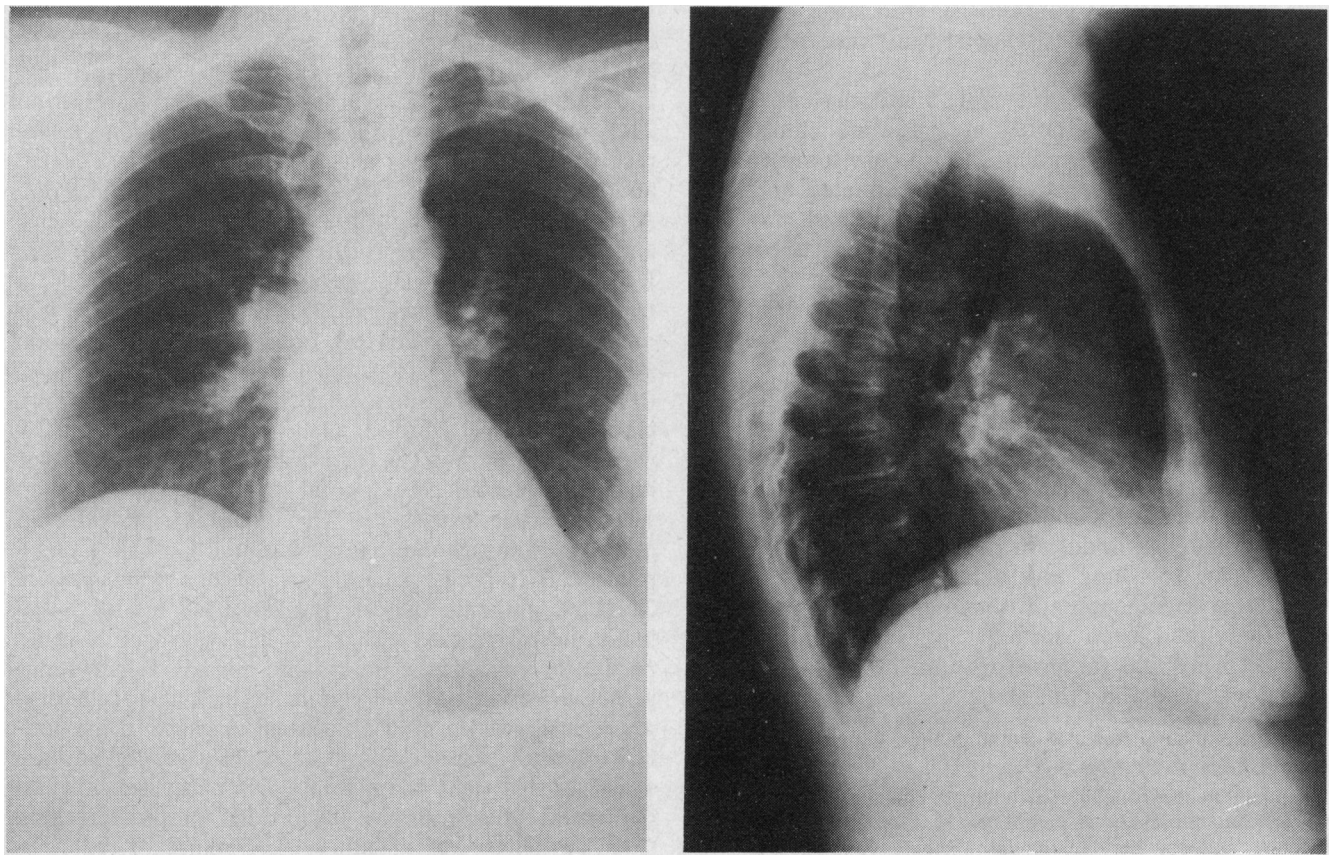

FIG. 1—Right hilar lymphadenopathy, small nodule in periphery of lower lobe of left lung and pathologic fracture of sixth left rib.

hypercalcemia related to malignant disease bone absorption occurs as a result of the production of parathyroid hormone or parathyroid-hormone-like hormones in a syndrome of pseudohyperparathyroidism. Ectopic production of parathyroid hormone has been reported in cases of squamous cell carcinoma of the lung or renal pelvis, hypernephroma, and carcinoma of the liver, breast, ovary or pancreas. Because the malignant cells are relatively inefficient at producing hormones, these tumours are usually not occult when hypercalcemia is noted. An osteoclast activating factor is released by certain lymphomas and in multiple myeloma.[3] Prostaglandins may mediate hypercalcemia in carcinomas of the breast, lung and kidney with or without direct bone involvement,[4,5] and peptides with direct osteolytic activity have been implicated in the metastasis of breast carcinoma. Some sarcomas produce a phosphaturic factor, which can cause a severe renal loss of phosphate, with occasional mild increases in the serum calcium concentration.

The patient's signs and symptoms were consistent with occult malignant disease, though it is possible that her anorexia, fatigue and weakness were directly attributable to the high serum calcium concentration. It is unlikely that the hypercalcemia was related to either a phosphaturic factor or an osteoclast activating factor: the normal serum phosphate concentration and the rarity of hemangiosarcoma rule out the former, and the negative results of bone marrow analysis and protein electrophoresis tend to rule out the latter. The absence of either diffuse osteopenia or discrete lesions on the skeletal roentgenograms and the high level of serum alkaline phosphatase, probably of bone origin, are also against myeloma as the diagnosis. The normal bone marrow and the absence of palpable lymphadenopathy rule out lymphoma. Lung cancer is an unlikely diagnosis. The nodule in the periphery of the lower lobe of the left lung, coupled with the right hilar lymphadenopathy, is more suggestive of metastatic disease from elsewhere. Breast cancer is also an unlikely diagnosis in view of the unremarkable physical findings. Other tumours associated with hypercalcemia, excluded in this patient because of the absence of pertinent physical and laboratory findings, include carcinomas of the liver, thyroid, bladder and ovary.

Table I—Causes of hypercalcemia in two series of hospitalized patients

Cause	Serum calcium concentration; no. of patients	
	> 2.8 mmol/l (11.3 mg/dl)[1]	> 2.6 mmol/l (10.4 mg/dl)[2]
Malignant disease	117	30
Hyperparathyroidism	104	11
Laboratory error	41	12
Vitamin D intoxication	37	4
Hyperthyroidism	12	–
Milk-alkali syndrome	12	3
Immobilization	7	1
Idiopathic hypercalcemia of infancy	3	–
Sarcoidosis	3	6
Dysproteinemia	2	–
Addison's disease	2	–
Dialysis	–	6
Uncertain	–	27

We are left, then, with the deduction that hypernephroma was the underlying malignant tumour in this case, accounting for the abnormalities shown by intravenous pyelography and ultrasonography, the pathologic fracture, the high level of serum calcium and the metastatic lesions shown on the chest roentgenogram. This tumour has been reported to cause hypercalcemia in three ways: through direct effects of bone metastases, through the development of pseudohyperparathyroidism in the absence of metastases, and through the action of prostaglandins. In our patient the first mechanism is the most likely: metastatic lesions were found in the ribs and pelvis by skeletal roentgenography. The serum phosphate concentration was within the normal range and, more important, the ratio of serum chloride (in millimoles per litre) to serum phosphate (in milligrams per decilitre) was 23.4, well below the range described by Palmer and colleagues[6] for parathyroid-hormone-dependent hypercalcemia (31.8 to 80.0); in this condition the higher ratio is thought to result from increased levels of serum chloride secondary to the wasting of renal bicarbonate induced by the hormone. In this case the serum bicarbonate level was 32 mmol/l, a high value, probably representing metabolic alkalosis secondary to the increased breakdown of bone and the subsequent increase in buffer capacity. In acute conditions alkalosis associated with dehydration can also account for a high level of serum bicarbonate.

Urinalysis revealed microscopic amounts of blood. The 3+ proteinuria reflected the presence of blood and a concentrated urine caused, we suspect, by the patient's low fluid intake. Granular casts are a nonspecific finding; they are seen in dehydrated patients and in others with congestive heart failure. The apparently normal level of blood urea nitrogen probably did not accurately reflect the patient's blood volume if we assume she was in the catabolic state suggested by the low level of serum albumin. The other tests of liver function gave normal results if we ascribe the higher level of alkaline phosphatase to osteoblastic activity related to metastatic disease, though it is possible that this enzyme was of ectopic origin as well. The slight rise in the level of serum glutamic pyruvic transaminase was not diagnostic, although hepatocellular enzyme abnormalities secondary to reactive hepatitis would not be unexpected. The level of serum sodium was at the lower limit of the normal range, perhaps reflecting the effect of an increased concentration of calcium on the renal tubule. The patient also suffered from the anemia of chronic disease, having a slightly low mean corpuscular volume and a slightly high corrected reticulocyte count. The rouleau formation in the blood smear was probably an artefact.

As mentioned, roentgenography showed a rib fracture, deterioration of the pubic ramus, and lung parenchymal and hilar metastases. The gravity and flow-dependent distribution of lesions was not visible, pos-

sibly because the patient had spent much of the time preceding her admission to hospital lying in bed. The pyelogram revealed a mass displacing the left kidney, which I believe represented the primary tumour, despite the normal appearance of the collecting system.

The slightly high level of carcinoembryonic antigen noted 7 months prior to admission, which is consistent with either cigarette smoking or the presence of adenomatous polyps, was a nonspecific finding and has been reported in 56% of one series of patients with confirmed hypernephroma.[7]

In conclusion, our patient presented with stage IV hypernephroma (that is, with distant metastases) and probably died as a result of progressive failure of the central nervous system secondary to hypercalcemia.

Clinical diagnosis

- Hypernephroma with metastases to lung and bone
- Hypercalcemia

Pathological discussion

Dr. Sheldon: In this case a number of findings could distract the diagnostician from an intuitive diagnosis. The surgical procedures, the adenomatous polyps and the equivocally raised level of carcinoembryonic antigen point to the gastrointestinal tract as a source of the complaints. The anemia, weight loss, fatigue, bone lesions, hypercalcemia and adenopathy, plus the course of the patient's condition in hospital, make the diagnosis of a malignant disease quite likely. The question remains as to what kind of tumour it was. The clue comes from the intravenous pyelogram, which shows a mass displacing the left kidney. An autopsy revealed that the patient had had renal cell carcinoma (hypernephroma) of the left kidney with metastatic nodules involving the lower lobes of both lungs, the hilar and mesenteric lymph nodes, the sixth left rib, the left lobe of the thyroid gland and the other kidney.

It is desirable to review renal cell carcinoma because new diagnostic procedures, including ultrasonography, scintiscanning, nephrotomography, angiography and needle aspiration, make it possible to diagnose adenocarcinoma of the kidney earlier. The degree of success in curing this disease is directly related to the tumour's size and extension beyond the kidney.

Hypernephroma is commonest in individuals over 50 years of age and is three times more common in men than in women. Its incidence in North America is 3.5 cases per 100 000 population, the same as the incidence of lung carcinoma in nonsmokers. (For those who smoke more than one pack a day the incidence of lung carcinoma is 217 per 100 000 population.) Though it constitutes only about 1% of all malignant diseases, excluding those of the skin, hypernephroma makes up 89% of all kidney tumours. We can hope that it will soon, like the kidney tumour of childhood, Wilms' tumour, be curable.

The signs and symptoms of hypernephroma vary considerably with the series reported (Table II),[10-12] but anemia, hematuria, flank pain and a palpable mass are the classic findings that suggest the diagnosis. Several studies have emphasized the systemic manifestations of hypernephroma (Table III).[12,13] In male patients a varicocele, due to spermatic vein obstruction, should suggest the appropriate diagnosis. Polycythemia, erythrocytosis, amyloidosis, Cushing's syndrome and high output cardiac failure are rare, but we continue to look for them and to associate them with adenocarcinoma of the kidney, the "internist's tumour".

Hypernephroma is usually diagnosed on the basis of the clinical presentation, with laboratory and radiologic findings confirming the presence of a renal mass. The abnormalities found by routine blood analysis may direct the clinician's investigation, as will a high erythrocyte sedimentation rate and a high serum haptoglobin level, seen in most cases, and a raised level of carcinoembryonic antigen, noted in more than half the patients with advanced disease. Urine cytology may not be helpful because of the relatively high frequency of false-negative results. Urinalysis yields abnormal results in only 70% of cases. When intravenous pyelography is used with nephrotomography hypernephroma can be identified in nearly 95% of cases. When urography with a high dose of contrast medium is used alone the only reliable diagnostic finding is invasion of the calyceal system, manifested by irregularity of the calyceal wall; there are associated

Table II—Signs and symptoms of hypernephroma in two series of cases

	Year of report; % of cases	
Signs and symptoms	1966[8]	1970[9]
Raised erythrocyte sedimentation rate	76–81	66
Anemia	–	64
Hematuria	60	32
Flank pain	50	24
Nonurinary symptoms	–	38
Palpable mass	40	34
Weight loss	25–35	22
Fever	25	13
"Classic triad"*	15	5
Polycythemia	1–5	5
Hypercalcemia	–	4

*Hematuria, flank pain and a palpable mass.

Table III—Systemic manifestations of hypernephroma[13]

Manifestation	% of cases
Raised erythrocyte sedimentation rate	56
Anemia	41
Hypertension (blood pressure > 150/100 mm Hg)	38
Cachexia, fatigue, weight loss	34
Pyrexia	17
Abnormal liver function	15
Raised serum alkaline phosphatase level	10
Hypercalcemia	6
Erythrocytosis	4
Neuromyopathy	3
Amyloidosis	2

intraluminal defects. Ultrasonography is also useful and has a diagnostic accuracy of about 95% for lesions 3 cm in diameter or greater, as does computer-assisted tomography.

The carcinoembryonic antigen level of 4.6 ng/dl deserves comment as it was only slightly above normal and therefore was misleading. Most adenomatous polyps do not give positive results when stained for this antigen. Marginally high levels of carcinoembryonic antigen in the serum can occur with such benign tumours as villous adenoma, particularly if the tumour has been present for more than a year (P. Gold: personal communication, 1979), and have also been reported in cases of pancreatitis, inflammatory bowel disease and alcoholic cirrhosis; smokers are frequently found to have high levels as well. Carcinomas in which levels of this antigen may be high include those arising in the pancreas (90%), liver, stomach, lung and breast (50%). High levels have also been reported in up to 56% of advanced cases of hypernephroma.[7] Serial measurements are more important than a single measurement that gives a slightly high value, and levels less than 20 ng/dl are more likely in benign disease.

It is useful to review the treatment of renal cell carcinoma because of the changing ideas about the disease's cause and pathogenesis, and because chemotherapy and radiation therapy are currently being added to the usual surgical management of the tumour.

The first operation to remove a renal cell carcinoma was successfully completed more than a century ago.[14] Since then the results of surgery have continually improved (Fig. 3) dependent on the stage and histologic grade of the tumour. If the improvement over the last two decades in the prognosis for children with Wilms' tumour gives any indication, hypernephroma may also be regarded as one of the malignant diseases in which, in future, early diagnosis may lead to a complete cure. Spontaneous remission has been documented in 60 cases (56 reported as of 1973).[13] This is of particular interest since immunocellular responses to hypernephroma have been shown in a number of cases, and treatment of one kindred with hyperimmune serum has been followed by remission of metastases.[11] Other explanations for the remission of this tumour have been its humoral dependence and its tendency to outgrow its vascular supply.

The widespread occurrence of simple benign adenomas of the kidney and the finding that such tumours are frequently multiple has raised questions of their relation to the adenocarcinomas such as this patient had. Hypernephromas arise from cells of the proximal convoluted tubules of the kidney (not, as Grawitz thought, from an adrenal rest), and are often histologically benign. We now believe that for patients whose disease involved the renal vein but did not show nodal metastasis the prognosis for survival 5 and 10 years after surgery is good. We also believe that size is the best criterion of malignancy for renal cell carcinoma; all tumours greater than 3 cm in diameter are treated as malignant, regardless of their histologic appearance.

The cause of these adenomas is still uncertain, but

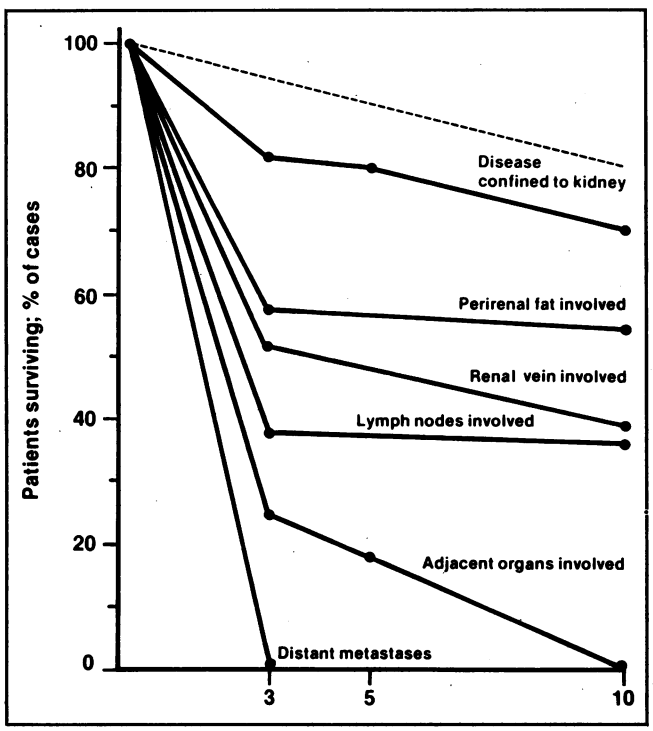

FIG. 3—Survival of patients following surgery to remove kidney tumours, at an average of 56 years, according to stage of the disease, compared with survival of the general population from age 56 to 66 (broken line). Reproduced from Robson and colleagues,[15] with permission from the authors and publisher, Williams & Wilkins, Baltimore.

Table IV—Factors by which the incidence rates of renal adenoma and renal adenocarcinoma are increased in men using various forms of tobacco[10]

Form of tobacco	Factor: Renal adenoma	Factor: Renal adenocarcinoma
Cigarettes (more than 10/d)	5.4	5.1
Pipe	3.1	10.3
Cigars	9.1	12.9
Chewing tobacco	5.1	4.8
Pipe, cigars and chewing tobacco combined	4.6	8.2
All forms of tobacco combined	5.4	5.4

the relation of renal adenoma and adenocarcinoma to smoking is shown in Table IV. Although the use of all forms of tobacco combined increases the incidence of the two types of tumour by the same factor, the use of pipes, cigars and chewing tobacco combined increases the incidence of carcinomas almost twice as much as it does the incidence of benign small adenomas. Pipe smoking alone increases the incidence of renal carcinoma more than three times as much as it increases the incidence of benign adenomas. The cause of these adenomas and carcinomas is still uncertain. The existence of virally induced kidney carcinomas in animals other than humans is well established.[16] However, to consider a virus as an inducer and tobacco as a promoter is speculation.

To return to this case, we assume that the renal cell adenocarcinoma was present and silently growing during the last 2 or 3 years of the patient's life, accounting for the symptoms that were attributed to gastrointestinal and perhaps cardiac disorders. This tumour must be considered in all people 50 years of age and over, particularly those with anemia, fever or hematuria, since early diagnosis offers the prospect of cure.

Pathological diagnosis

- Renal cell carcinoma of the left kidney, with metastases to the right kidney, lower lobe of both lungs, hilar and mesenteric lymph nodes, sixth left rib and left lobe of the thyroid gland.
- Acute bronchopneumonia.

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